COMPARISON OF APPROACHES TO *ent*-MORPHINE *via* RADICAL, CATIONIC, AND HECK-TYPE CYCLIZATIONS

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

3-(2-{6*S*-(2-Bromo-6-methoxyphenoxy)-5*S*-[*tert*-butyl(dimethyl)silyloxy)cyclohex-1-en-1-yl}-ethyl)oxazol-2(3*H*)-one **14** was subjected to Heck cyclization conditions to afford dibenzofuran derivative **16**. The comparison of stepwise *vs* cascade approaches to **8** *via* radical, cationic, and Heck-type cyclizations is discussed.

Key words: Morphine; Heck reaction; Alkaloids; Biooxidation; Total synthesis; Palladium; Cascade cyclizations.

We are continuing to focus our attention on devising an efficient synthesis of morphine (**1**)[1,2]. During the last eight years we have investigated several chemoenzymatic approaches, all based on the general plan described in Scheme 1. The disconnection shown is based on the anticipation that the absolute stereochemistry of ring C can be derived from diene diol **2**, prepared by toluene dioxygenase-mediated biooxidation of β-halo arenes of type **3** (ref.[3]). Since the pioneering work of Gibson, who elucidated the degradation pathway of arenes by the soil bacterium *Pseudomonas putida*[4], efficient recombinant organisms for the transformation of **3** to **2** have become available[5], as has a general procedure for the production of various metabolites[6]. In addition, the expression of catechol dehydrogenase, the enzyme for the second step of the degradation pathway, enables the conversion of bromobenzene (**5**), *via* its diene diol, to bromocatechol, which after methylation becomes our synthon (**4**) for morphine's aromatic A ring[7].

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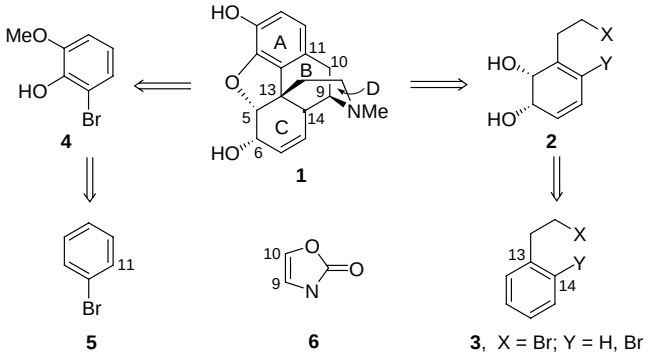
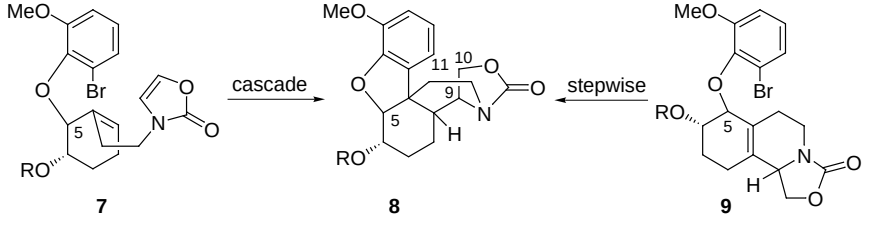
Finally, the carbons at positions 9 and 10 as well as the *N*-methyl group can be derived from oxazol-2(3*H*)-one (**6**), prepared by anodic oxidation[7,8].



SCHEME 1
Chemoenzymatic approach to morphine

Of the two strategies tested (for the natural series), the first was a radical cascade from **7** to pentacycle **8** (Scheme 2), whose C10–C11 closure would lead to the complete morphinan skeleton. Because of the lack of stereoselectivity inherent in this approach, we executed a stepwise sequence from **2** (X = Y = Br) *via* isoquinoline derivative **9**, also obtained with low stereocontrol[7]. The closure of **9** to **8** followed by further elaboration led to the complete morphine skeleton (in the *ent*-series)[8]. The synthesis of isoquinoline derivatives **9** in both enantiomeric series has been improved subsequently by the use of acid-catalyzed iminium-ion closures[9] and electrochemical methods[10] for the synthesis of precursors.



SCHEME 2
Cascade *vs* stepwise cyclizations. Stereochemistry at C5 is α (natural) or β (*ent*)

Herein we report the details of a stepwise approach in which the quaternary center at C13 is generated by a rare intramolecular Heck reaction[11], and we compare it to the corresponding cascade from a precursor such as **7**.

EXPERIMENTAL

All non-hydrolytic reactions were performed under an argon atmosphere in solvents dried according standard procedures. Whatman silica gel 60F-254 plates were used for analytical thin-layer chromatography (TLC). Fisher silica gel (grade 60, 200–425 mesh) was used for flash column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 300 MHz instrument in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in ppm (δ scale) relative to deuteriochloroform (7.24 and 77 ppm for ^{1}H and ^{13}C spectra, respectively), coupling constant (*J*) in Hz. All 2D NMR experiments were performed on a Varian Unity 500 MHz instrument. Mass spectra were recorded on a Finnigan Mat 95 Q mass spectrometer. IR spectra (wavenumbers in cm^{-1}) were obtained on a Perkin–Elmer 1600 Series instrument. Optical rotations were measured on a Perkin–Elmer polarimeter; $[\alpha]_b$ values are given in 10^{-1} deg cm^2 g^{-1}.

(7*S*,8*S*,10b*S*)-7-(2-Bromo-6-methoxyphenoxy)-8-[*tert*-butyl(dimethyl)silyloxy]-5,6,7,8,9,10-hexahydro-1*H*-oxazolo[4,3-*a*]isoquinolin-3-one (**11**)

To a stirred solution of **10** (0.040 g, 0.12 mmol) and 6-bromo-2-methoxyphenol (0.067 g, 0.35 mmol) in dry THF (0.50 ml) at 0 °C was added a solution of the Mitsunobu reagent, which was previously prepared by the addition of diethyl azodicarboxylate (DEAD) (0.35 ml, 0.063 mmol) to a stirred solution of Bu_3P (0.088 ml, 0.35 mmol) in dry THF (0.5 ml) at 0 °C, and stirred at the same temperature for 15 min. The reaction mixture was allowed to warm to room temperature. After 14 h, the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc 9 : 1) to yield pure **11** (0.033 g, 53%) as a colorless oil; R_F 0.48 (hexanes–EtOAc 1 : 1); $[\alpha]_D^{31}$ +75.5 (*c* 1.0, CH_2Cl_2). IR (KBr): 2 928, 2 855, 1 759, 1 583, 1 471, 1 451, 1 259, 1 222, 1 083, 1 031, 836, 773. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.13 (dd, *J* = 7.9, 1.6, 1 H); 6.92 (t, *J* = 8.0, 1 H); 6.85 (dd, *J* = 8.0, 1.6); 4.49 (dd, *J* = 8.5, 8.4, 1 H); 4.27 (m, 2 H); 3.98 (m, 3 H); 3.83 (s, 3 H); 3.10 (td, *J* = 11.8, 4.5, 1 H); 2.66 (m, 1 H); 2.20 (m, 3 H); 1.73 (m, 2 H); 0.73 (s, 9 H); –0.17 (s, 3 H); –0.21 (s, 3 H). ^{13}C NMR (75 MHz): 157.4, 153.3, 144.3, 132.2, 126.1, 125.1, 124.9, 118.0, 111.4, 79.4, 67.0, 66.3, 55.6, 38.3, 25.6, 25.4, 24.8, 19.9, 17.9, –5.2, –5.3. HR MS: calculated for $C_{24}H_{35}BrNO_5Si$ 524.1468, found 524.1450.

(3a*R*,6*S*,6a*S*,11b*R*)-6-[*tert*-Butyl(dimethyl)silyloxy]-8-methoxy-3,3a,5,6,6a,11b,12,13-octahydro-1*H*-benzo[2,3][1]benzofuro[4,3*a*-*c*][1,3]oxazolo[3,4-*a*]pyridin-1-one (**13**)

A flame-dried round-bottomed flask equipped with a condenser was charged with **11** (6 mg, 0.0012 mmol), $Pd(PPh_3)_4$ (14 mg, 0.00012 mmol), PPh_3 (1 mg, 0.00048 mmol), Proton Sponge® (10 mg, 0.0048 mmol), and toluene (5.0 ml). The reaction mixture was heated at reflux for 48 h, then the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc 9 : 1) to yield pure **13** (3 mg, 57%) as a colorless oil; R_F 0.41 (hexanes–EtOAc 1 : 1); $[\alpha]_D^{26}$ +32.0 (*c* 1.0, CH_2Cl_2). IR (KBr): 2 961.4, 2 925.5, 2 851.6, 1 755.0, 1 619.1, 1 586.0, 1 488.4, 1 462.0, 1 378.3, 1 278.3, 1 115.8. ^{1}H NMR (500 MHz, $CDCl_3$): 7.07 (dd, *J* = 7.1, 1.8, 1 H); 6.85 (dd, *J* = 8.2, 7.3, 1 H); 6.82 (dd, *J* = 8.2, 1.6, 1 H); 5.42 (ddd *J* = 5.3, 3.4, 2.1, 1 H); 4.70 (t, *J* = 7.8); 4.44 (dd, *J* = 8.4, 7.6, 1 H); 4.39 (d, *J* = 5.3, 1 H); 4.38 (dd, *J* = 8.4, 7.8, 1 H); 4.27 (q, *J* = 4.8, 1 H); 3.91 (ddd, *J* = 13.8, 6.0, 1.6, 1 H); 3.88 (s, 3 H); 3.58 (td, *J* = 13.4, 3.9, 1 H); 2.45 (dq, *J* = 17.5, 3.6, 1 H); 2.21 (dt, *J* = 17.5, 5.2, 1 H); 2.11 (td, *J* = 13.3, 6.1, 1 H); 1.94 (ddd, *J* = 13.1, 3.4, 1.4, 1 H);

0.88 (s, 9 H); 0.10 (s, 3 H); 0.05 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 156.9, 146.9, 145.6, 133.3, 132.6, 121.3, 118.2, 117.9, 112.1, 98.5, 65.0, 56.1, 56.0, 53.8, 48.2, 37.8, 36.2, 29.4, 25.8, 18.1, –4.7, –5.1. HR MS: calculated for $C_{24}H_{35}NO_5Si$ 445.2284, found 445.2223.

3-(2-{6*S*-(2-Bromo-6-methoxyphenoxy)-5*S*-[*tert*-butyl(dimethyl)silyloxy)-cyclohex-1-en-1-yl}ethyl)oxazol-2(3*H*)-one (**14**)

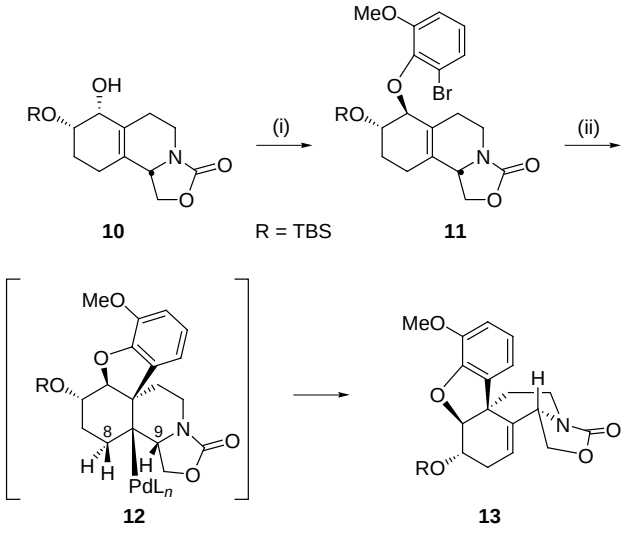
To a stirred solution of 3-(2-{5*S*-[*tert*-butyl(dimethyl)silyloxy)-6*R*-hydroxycyclohex-1-en-1-yl}-ethyl)oxazol-2(3*H*)-one[8] (0.26 g, 0.78 mmol) and 6-bromo-2-methoxyphenol (0.16 g, 0.82 mmol) in dry THF (1.0 ml) at 0 °C was added a solution of the Mitsunobu reagent, which had been previously prepared by the addition of DEAD (0.28 ml, 1.6 mmol) to a stirred solution of Bu_3P (0.39 ml, 1.6 mmol) in dry THF (1.0 ml) at 0 °C, and stirred at the same temperature for 15 min. The reaction mixture was allowed to warm to room temperature. After 18 h, the solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc 9 : 1) to yield pure **14** (0.30 g, 73%) as a colorless oil; R_F 0.53 (hexanes–EtOAc 1 : 1); $[\alpha]_D^{30}$ +54.0 (*c* 1.0, CH_2Cl_2). IR (KBr): 2 955, 2 924, 2 851, 1 747, 1 693, 1 650, 1 582, 1 555, 1 469, 1 404, 1 257, 1 222, 1 081, 1 031, 967, 835, 768. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.15 (dd, *J* = 8.1, 1.6, 1 H); 6.93 (t, *J* = 8.1, 1 H); 6.87 (dd, *J* = 8.2, 1.5, 1 H); 6.67 (d, *J* = 2.2, 1 H); 6.64 (d, *J* = 2.0, 1 H); 5.76 (d, *J* = 5.2, 1 H); 4.50 (m); 3.99 (dt, *J* = 4.0, 2.0, 1 H); 3.90 (dt, *J* = 13.8, 6.9, 1 H); 3.86 (s, 3 H); 3.69 (ddd, *J* = 13.7, 7.5, 6.1, 1 H); 2.75 (dt, *J* = 13.8, 6.9, 1 H); 2.47 (dt, *J* = 14.0, 7.0, 1 H); 2.23 (m); 2.18 (m); 1.98 (m); 1.67 (m); 0.73 (s, 9 H); –0.16 (s, 3 H); –0.19 (s, 3 H). ^{13}C NMR (75 MHz): 155.8, 153.3, 144.0, 132.6, 129.2, 126.3, 125.2, 124.8, 118.2, 117.3, 111.5, 79.2, 67.1, 55.7, 42.8, 34.8, 25.6, 24.8, 20.6, 18.1, –5.2. HR MS: calculated for $C_{24}H_{35}BrNO_5Si$ 524.1468, found 524.1420.

3-(2-(5a*S*,6*S*,9a*R*)-6-[*tert*-Butyl(dimethyl)silyloxy)]-4-methoxy-5a,6,7,9a-tetrahydro-benzo[*b*][1]benzofuran-9a-yl}ethyl)oxazol-2(3*H*)-one (**16**)

A flame-dried heavy-walled Pyrex tube under static argon atmosphere was charged with **14** (40 mg, 0.08 mmol), $Pd(PPh_3)_4$ (9 mg, 0.008 mmol), PPh_3 (8 mg, 0.03 mmol), triethylamine (0.02 ml, 0.15 mmol), and toluene (5.0 ml). The tube was capped with a self-sealing, rubber-lined cap and heated to 120 °C. After 19 days, the solvents were evaporated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (hexanes–EtOAc 9 : 1, eluted 10 times) to yield **16** (4.4 mg, 13%) as a colorless oil, along with 53% recovered starting material **14**; R_F 0.52 (hexanes–EtOAc 1 : 1); $[\alpha]_D^{25}$ +59.0 (*c* 1.0, CH_2Cl_2) (Note: this sample was shown to be 74% pure by HPLC in MeOH–H_2O). ^{1}H NMR ($CDCl_3$, 500 MHz): 6.86 (dd, *J* = 8.1, 7.6, 1 H); 6.76 (dd, *J* = 8.2, 1.1, 1 H); 6.73 (d, *J* = 2.0, 1 H); 6.72 (dd, *J* = 7.7, 1.1, 1 H); 6.38 (d, *J* = 2.1, 1 H); 5.76 (dt, *J* = 10.0, 1.3, 1 H); 5.71 (ddd, *J* = 9.9, 4.3, 3.4, 1 H); 4.56 (d, *J* = 6.6, 1 H); 4.04 (ddd, *J* = 7.1, 6.7, 4.8, 1 H); 3.86 (s, 3 H); 3.65 (ddd, *J* = 14.0, 10.1, 6.3, 1 H); 3.50 (ddd, *J* = 14.2, 10.6, 5.8, 1 H); 2.30 (dt, *J* = 16.9, 4.7, 1 H); 2.11 (m, 1 H); 2.07 (m, 1 H); 0.91 (s, 9 H); 0.14 (s, 3 H); 0.06 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): 155.6, 146.0, 145.3, 134.4, 129.3, 127.7, 124.4, 122.1, 115.6, 115.1, 89.8, 67.8, 56.0, 49.4, 40.7, 38.7, 30.1, 25.9, 18.3, –4.6, –5.4. HR MS: calculated for $C_{24}H_{34}NO_5Si$ 444.2206, found 444.2173.

RESULTS AND DISCUSSION

In a recent communication[11] we disclosed the results of an unusual Heck cyclization of aryl ether **11** (Scheme 3), prepared from the known isoquinoline derivative **10** (ref.[9]) by a simple Mitsunobu inversion. It cyclized smoothly to pentacycle **13**, which contains some of the structural elements of neopine-type alkaloids.



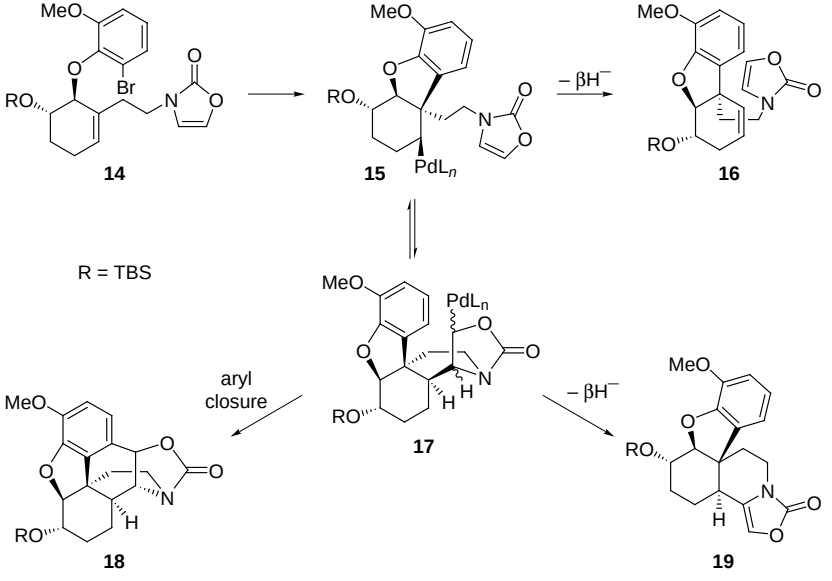
SCHEME 3
Reagents and conditions: (i) Bu_3P, DEAD, bromoguiacol, THF (53%); (ii) $Pd(PPh_3)_4$, Proton Sponge, toluene, reflux (57%)

The attainment of this material (in the *ent*-series with respect to C5, C13, and in the natural series with respect to C14) offered several new possibilities for approaches to morphine. The choice of carbamate **11** was prudent despite its "incorrect" configuration at C9 as β-hydride elimination could occur from either C8 or C9. Heck cyclizations are rare for tetrasubstituted olefins: the only precedent of which we were aware was in a model study published by Cheng[12a], who has recently completed the synthesis of the intact morphine skeleton[12b,12c].

Unlike in Cheng's model study, we observed only a regioselective elimination to **13**. In the actual precursors to either natural or *ent*-morphinans, the C9 hydrogen will always be *trans* to the organopalladium species. The most significant event in our successful Heck closure is the "return" of the correct oxidation state into the ring C of morphine. The neopine-type ole-

fin can be easily manipulated, following the C10–C11 closure, into the required C7–C8 position in codeinone, for example, as recently demonstrated by Rice[13].

Encouraged by this result we wished to compare the Heck closure of **11** to **13**, in which there are no stereochemical consequences at C14, with a similar cascade closure we previously accomplished with **7**. An outline of possible events that would be expected is shown in Scheme 4. Carefully considering Heck catalysis[14,15], we concluded that the reaction performed under conditions favoring β-hydride elimination from **15** was not conducive to a cascade reaction sequence. Instead we selected two sets of experimental conditions: one that was expected to yield **16** and another in which the choice of the palladium ligands would slow down the elimination and favor production of **17**. Beyond **17** the fate seems unpredictable: even though C14 must be correctly set after the initial Heck addition, the stereochemistry at C9 is uncertain, as is the potential for either direct Heck reaction onto the arene in **18** or elimination to enamine **19**.



SCHEME 4
Projected outcome of the cascade Heck cyclization

Several Heck cascade cyclizations with competing β-hydride eliminations are described in the literature[16–18]. At first we used conditions similar to those in de Meijere's domino tetracyclization[17]. Model substrate **14** was

treated with 10 mole % $Pd(OAc)_2$, 20 mole % (*o*-Tol)$_3$P, two equivalents of triethylamine, in acetonitrile at 120 °C. After 4 days, the reaction mixture still contained mostly starting material (with 80% recovery). Because the palladium species precipitated out of the reaction, the reaction was repeated with 30 mole % $Pd(OAc)_2$, 60 mole % (*o*-Tol)$_3$P, and 2 equivalents Et_3N in acetonitrile at 120 °C. After 14 days, the reaction mixture still contained mostly starting material; however, an impurity in the recovered starting material showed features of the β-hydride eliminated product **16**. NMR characterization was inconclusive because of the miniscule amount of **16**, but we were able to identify it (overlapping with unreacted starting material) in the reaction mixture, and the presence of **16** was confirmed by HPLC-MS analysis.

Grotjahn[16] has shown that in aqueous media insertion into an alkene is favored over β-hydride elimination with the use of phenanthroline ligands. Accordingly we treated substrate **14** with 10 mole % $Pd(OAc)_2$, 20 mole % 1,10-phenanthroline, 1 equivalent Bu_4NBr, and 2.5 equivalents K_2CO_3 in a 1 : 1 mixture of ethanol and water at 80 °C. Nevertheless, after 7 days most of the starting material was still unreacted, and there was a small amount of the hydrolyzed carbamate present.

In an effort to elicit at least the formation of **16**, the reaction was performed under conditions similar to those that provided **13**. Aryl bromide **14** was treated with 10 mole % $Pd(PPh_3)_4$, 40 mole % PPh_3, and 2 equivalents Et_3N in toluene at 120 °C. After 19 days, the reaction was worked-up and products were separated by preparative thin-layer chromatography (10 elutions). Olefin **16** was isolated in 13% yield along with 53% recovered starting material.

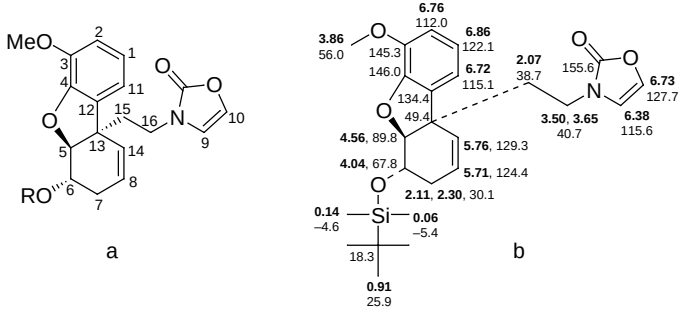


FIG. 1

a Numbering of **16** with respect to morphine; b assignment of H1 (bold) and C13 (underlined) chemical shifts for **16**

The structure elucidation of **16** was carried out by a combination of DQCOSY, gradient HMQC and HMBC, and NOESY experiments. The ^{1}H and ^{13}C chemical shift assignments, together with the morphine-like numbering, are shown in Fig. 1. The long-range proton–carbon correlations proved the structural integrity of **16**. That the new bond C12–C13 had been formed was demonstrated by the long-range coupling of C12 with the protons on C5 and C15 and that of C13 with the proton on C11.

We do not yet understand the difference between the successful formation of **13** (57%) in one case and the lower yield of **16** (13%) in the other. It is possible that the rate of Heck cyclization of **14** is hindered by strong chelation of the oxazol-2(3*H*)-one[19]. The oxidative addition product of **14**, in particular **15**, may also be bound by the carbamate, which impedes further cyclizations. Such chelation is not possible in the isoquinoline derivative **11**, nor was it observed in Cheng's model; in both cases good yields were observed. Future experiments will focus on repetition of these experiments with substrates that contain olefinic functionalities (such as *N*-methyl-*N*-vinyl groups) with fewer chelating properties than the oxazol-2(3*H*)-one ring.

In conclusion, both the radical cascade of **7** and the radical closure of **9** gave poor control of the C14 stereochemistry. The stepwise radical cyclization *via* **9** also resulted in poor stereocontrol at C9. The acyliminium closures leading to **9** furnish the correct stereochemistry at C9 albeit in low yield. Because the Heck cyclization in either enantiomeric series can, unlike its radical counterpart, lead to full control of stereochemistry at C14 (and perhaps at C9 as well), we are pursuing them further and will report the results in due course.

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REFERENCES AND NOTES

1. a) Hudlicky T., Butora G., Fearnley S. P., Gum A. G., Stabile M. R. in: *Studies in Natural Product Chemistry* (Atta-ur-Rahman, Ed.), Vol. 18, p. 43. Elsevier, Amsterdam 1996; b) Maier M. in: *Organic Synthesis Highlights II* (H. Waldman, Ed.), p. 357. VCH, Weinheim 1995; c) Novak B., Hudlicky T., Mulzer J., Trauner D.: *Curr. Org. Chem.* **2000**, *4*, 343.
2. For review of the history of morphine structure elucidation see: Butora G., Hudlicky T. in: *Organic Synthesis: Theory and Applications* (T. Hudlicky, Ed.), Vol. 4, p. 1. JAI Press, Greenwich (CT) 1998.
3. For recent reviews on the use of metabolites of aromatic hydrocarbons in synthesis see: a) Hudlicky T., Gonzalez D., Gibson D. T.: *Aldrichim. Acta* **1999**, *31*, 35; b) Boyd D. R.,

Sheldrake G. N.: *Nat. Prod. Rep.* **1998**, *15*, 309; c) Hudlicky T., Reed J. W. in: *Advances in Asymmetric Synthesis* (A. Hassner, Ed.), Vol. 1, p. 271. JAI Press, Greenwich (CT) 1995.
4. a) Gibson D. T., Koch J. R., Schuld C. L., Kallio R. E.: *Biochemistry* **1968**, *7*, 3795.; b) Resnick S. M., Lee K., Gibson D. T.: *J. Ind. Microbiol. Biot.* **1996**, *17*, 438.
5. Zylstra G. J., Gibson D. T.: J. Biol. Chem. **1989**, 264, 14940.
6. Hudlicky T., Stabile M. R., Gibson D. T., Whited G. M.: *Org. Synth.* **1999**, *76*, 77.
7. Butora G., Fearnley S. P., Gum A. G., Stabile M. R., Abboud K., Hudlicky T.: *Tetrahedron Lett.* **1996**, *37*, 8155.
8. Butora G., Hudlicky T., Fearnley S. P., Stabile M. R., Gum A. G., Gonzalez D.: *Synthesis* **1998**, 665.
9. Bottari P., Endoma M. A., Hudlicky T., Ghiviriga I., Abboud K. A.: *Collect. Czech. Chem. Commun.* **1999**, *64*, 203.
10. Endoma M. A., Butora G., Claeboe C. D., Hudlicky T.: *Tetrahedron Lett.* **1997**, *38*, 8833.
11. For preliminary account of parts of this work see: Frey D. A., Duan C., Hudlicky T.: *Org. Lett.* **1999**, *1*, 2085.
12. a) Cheng C. Y., Liou J. P., Lee M. J.: *Tetrahedron Lett.* **1997**, *38*, 4571; b) Lee M. J., Cheng C. Y.: Presented at *219th ACS National Meeting, San Francisco, March 27, 2000*, Abstract No. 305; c) Liou J. P, Cheng C. Y.: Presented at *219th ACS National Meeting, San Francisco, March 27, 2000*, Abstract No. 333.
13. Coop A., Rice K. C.: *Tetrahedron* **1999**, *55*, 11429.
14. Heck reviews: a) Heck R. F.: *Org. React.* **1982**, *27*, 345; b) Crisp G. P.: *Chem. Soc. Rev.* **1998**, *27*, 427; c) Hong Y. H., Kado N., Overman L. E.: *J. Am. Chem. Soc.* **1993**, *115*, 11028; d) Bräse S., de Meijere A. in: *Metal-Catalyzed Cross-Coupling Reactions* (F. Diederich and P. J. Stang, Eds), p. 99. Wiley–VCH, Weinheim 1998.
15. We are indebted to Professor Armin de Meijere for helpful discussions of experimental conditions.
16. Grotjahn D. B., Zhang X.: *J. Mol. Catal. A: Chem.* **1997**, *116*, 99.
17. Schweizer S., Song Z. Z., Meyer F. E., Parsons P. J., de Meijere A.: *Angew. Chem.* **1999**, *111*, 1550.
18. Herrmann W. A., Brossmer K., Öfele C. P., Resinger T.: *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
19. We are grateful to Professor Paul A. Wender for insightful discussion of this item.